CASE REPORT

Alleviation of extrapyramidal side effects upon switching from risperidone to paliperidone

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Abstract

Paliperidone is a new second generation antipsychotic; in terms of pharmacology, it is an active metabolite of risperidone. Compared to risperidone, paliperidone should thus show more stable occupation of dopamine receptors in the brain, which on one the hand may lead to increased antipsychotic efficacy, and on the other hand to reduced incidence of adverse extrapyramidal effects. The case report describes alleviation of Parkinson's syndrome induced by risperidone by switching to paliperidone in a young man with a new occurrence of a paranoid schizophrenia episode. Thanks to its clinical efficacy, paliperidone is ranked among the most successful second generation antipsychotics with reduced extrapyramidal symptomatology.

Introduction

Paliperidone is a new second generation antipsychotic; in terms of pharmacology, it is an active metabolite of risperidone. Paliperidone (9-hydroxyrisperidone) is a dopamine D_2 and serotonin 5-HT_{2A} receptor antagonist and thus it is classified in the group of atypical antipsychotic SDA (serotonin and dopamine antagonists). It also blocks alpha 1 and alpha 2 adrenergic receptors and histamine H_1 receptors to a lesser extent. On the other hand, paliperidone shows no affinity to muscarinic cholinergic or beta-adrenergic receptors (Yang & Plosker 2007). It is supplied in the innovative drug form OROS (Oral Osmotic System) that ensures stable release of the effective substance during 24 hours, thus preventing plasma level fluctuations (Yang & Plosker 2007). Unlike risperidone, paliperidone should thus show more stable occupation of dopamine receptors in the brain, which on the one hand may lead to increased antipsychotic efficacy, and on the other hand to reduced incidence of adverse effects, such as in particular hyperprolactinemia or extrapyramidal symptoms (Švestka & Doležal 2007). The case report describes a positive experience with the subsiding of adverse extrapyramidal symptoms by switching from risperidone to paliperidone in a patient with the first attack of paranoid schizophrenia.

Mr. A. characterizes himself as a withdrawn, pedantic, meticulous person. However, in the course of time he ceased to mind; he socialized with no one without any actual complaints. About one month ago, people around him started saying he was a homosexual, reportedly only because he has never had a female partner. Mr. A. naturally minds this. Moreover, this information also appears on television, they broadcast programmes about him where the editor winks at him and gives signs that she knows, and that she is going to spread it all around the world. It bothers him and moreover he is very much ashamed for this situation. He would like to stop this somehow, but does not

know how. They know it about him at work, too, his colleagues talk about it, he can tell from how they always laugh whenever he enters the door. While in a tram, he hears how people scream at him, how they laugh. All this happens in his head where he hears amplified sounds and voices of the surroundings, it causes terrible confusion to him. He is afraid because people watch him, take turns around him, he must pay attention constantly to what is happening, they probably want to hurt him. He sleeps poorly, cannot concentrate, feels tired. He is convinced that all this is real.

As for Mr. A.'s medical history, positive psychiatric heredity in terms of anxious conditions among his nearest relatives is worth mentioning. Physically, Mr. A. is healthy, has not been taking any drugs. He is not aware of any perinatal pathology, he remembers his childhood with pleasure, but already then he reports to have been quite withdrawn and therefore not having many friends. His withdrawn nature deepened even further during puberty. He has finished secondary education; at present, Mr. A. works as a porter; he feels comfortable with working with minimal social contacts. He describes himself as a recluse, introvert who likes reading or going for walks in nature. Mr. A. lives with his parents and evaluates their coexistence as contented. No elevated abusus of psychoactive substances exceeding the framework of acceptable social consumption was shown.

Upon admission to our medical institution, especially paranoid persecutory delusion production dominated, as well as massive imperative auditory hallucinations. The patient's mood was rather plain, he could not keep eye contact, loss of nonverbal communication was apparent with flattened emotivity and hypomimia. His psychomotor speed was slowed down. Coherent thinking persisted; however, it was sticking, poor in content, with loosened associations, intermittent paralogies and abstraction disorder. Especially schizoid character traits were apparent in the patient's personality. Although basic cooperation with the patient was preserved, virtually no insight in the disease existed.

Shortly upon admission to the bed ward, massive intrapsychic tension became accentuated, conditioned by strongly expressed productive psychotic symptomatology. The patient thus had to be medicated with intramuscular cisclopenthixol acutard in two 100mg doses in the space of 48 hours. Subsequently, the patient was switched to risperidone monotherapy with the daily dose titrated gradually from 2 mg to 4 mg pro die; clonazepame in daily dose up to 6 mg was chosen as accompanying therapy for anxiety and inner tension. Productive psychotic symptomatology subsided considerably during the first week of treatment; the patient was able to engage in common therapeutic activities at the department, and clonazepame was discontinued gradually.

In the third week of treatment, the patient started complaining about feelings of being slowed down, of deteriorated motor coordination, and mild hand tremor. Hypokinetic rigid syndrome as part of pharmacologically induced Parkinson's syndrome was found by clinical examination. An antiparkinsonic was administered immediately (biperidene in daily dose 2 mg) and paliperidone dosed 9 mg pro die. Subsequently, risperidone was discontinued by quick titration during 4 days. In spite of this rapid antipsychotic switching, the patient's clinical condition remained stable. Considerable subsiding of the hypokinetic rigid syndrome was observed 1 week after paliperidone discontinuation, making it possible to discontinue biperidene. The hypokinetic rigid syndrome disappeared completely after 2 weeks of paliperidone treatment; clinically, good-quality remission of the psychotic disease was moreover preserved.

The case report describes alleviation of risperidone-induced Parkinson's syndrome by switching to paliperidone in a young man with a new episode of paranoid schizophrenia. Extrapyramidal side effects occur frequently especially in patients in initial phases of schizophrenia who are more sensitive to them than patients in more advanced stages (Salimi *et al* 2009). Paliperidone should be the first-line substitution alternative in patients who develop Parkinson's syndrome or other extrapyramidal symptoms while on risperidone, considering the very similar pharmacodynamic profile of both antipsychotics and associated low risk of clinical condition destabilization. Incidence of extrapyramidal symptoms in studies with paliperidone was low; these symptoms occurred in 5% patients on paliperidone in the dosage 3 mg/day and in 10% of patients in the dosages 9 and 15 mg/day. Accompanying anticholinergic medication had to be used when administering paliperidone in daily dosages 3, 9, and 15 mg in 9%, 23%, and 15% patients compared to 10% on placebo (Davidson *et al* 2007). Virtually identical results were reported also in Marder's study where paliperidone in daily dosage 6 mg showed no difference compared to placebo in terms of inducing extrapyramidal symptoms. Anticholinergic comedication was used in 14% patients on paliperidone 6 mg/day, in 9% with 12 mg pro die, and in 16% on placebo, and in 12% on olanzapine (Marder *et al* 2007). Extrapyramidal symptomatology thus occurs approximately 2 times more often on paliperidone than on placebo. EPS incidence was comparable to placebo in 6 week studies using recommended daily dosage 6 mg. With higher daily dosages 9 mg and 12 mg, EPS was observed in 25% and 26% patients compared to 1% on placebo. Incidence of extrapyramidal symptomatology increases with rising daily dose of paliperidone (Owen 2007; Švestka & Doležal 2007).

It should be certainly considered detrimental that direct comparison of paliperidone and risperidone has not been performed so far. Only virtual informative comparison of both drugs is available. Placebo-controlled studies with paliperidone and risperidone (N=1103) were searched in the manufacturer's database. Paliperidone was administered in daily dosages

6–12 mg/day and risperidone 4–6 mg pro die (Schooler at al 2006). The efficacy of both placebo groups (with paliperidone and risperidone) was compared in the first place, which showed no difference in affecting the total PANSS score (Positive and Negative Syndrom Scale, Kay *et al* 1987). Subsequently, "virtual" comparison of paliperidone and risperidone was done. Both antipsychotics showed no difference in terms of therapeutic efficacy based on total PANSS score changes and also based on the numbers of patients who finished the studies (67.6% for paliperidone and 65.5% for risperidone). Comparison of paliperidone in daily dosage 6–12 mg to risperidone in lower daily dosages 2–4 mg revealed that the tested antipsychotic led to significantly higher reduction of the total PANSS score. Incidence of adverse effects was similar for both antipsychotics, while only an increase in weight was significantly higher after risperidone treatment (Švestka & Doležal 2007).

Next to clozapine, paliperidone is also a single antipsychotic described to adapt impaired cortical inhibition during antipsychotic treatment (Prikryl *et al* 2009). Impaired cortical inhibition is considered one of biological markers of schizophrenia (Daskalakis *et al* 2002). Its adjustment, expressed as extension of one neurophysiological parameter, the cortical silent period, is contributed to the function of $GABA_B$ receptors. These are metabotropic receptors that increase potassium concentrations and cause hyperpolarization of postsynaptic neurons (Franek 2004). Facilitation of $GABA_B$ receptor mediated neurotransmission can be therefore speculated to stand behind the antipsychotic effect and low incidence of extrapyramidal side effects of paliperidone similarly as in clozapine.

Introducing paliperidone in practical use represents a considerable innovation of existing antipsychotics belonging to the group of serotonin and dopamine antagonists (SDA), particularly the new galenic form. With its clinical efficacy, paliperidone is ranked among the most successful second generation antipsychotics with a lower incidence of extrapyramidal symptomatology (Švestka & Doležal 2007).

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